Evaluation of dual-acting PIM/PI3K inhibitor IBL-302 in preclinical breast cancer models

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INTRODUCTION

Activating PIK3 mutations have been identified in more than 30% of breast cancers. These mutations have been associated with resistance to trastuzumab a HER2-binding monoclonal antibody. PIM kinase expression has been shown to be markedly elevated in PI3K treated breast cancer samples suggesting that it could be a major resistance pathway for PI3K inhibitors in breast cancer, potentially limiting their clinical utility. IBL-302 is a novel molecule that inhibits both PI3K and PIMI signaling. This mechanism of action could afford significant benefit in the treatment of breast cancer.

AIMS

The primary objective of this study was to evaluate IBL-302 in preclinical in-vitro / in-vivo breast cancer models.

STRUCTURE OF IBL-302 – A NOVEL PIM/PI3K INHIBITOR

In conclusion,

IBL-302 IC50 in 40 Breast Cancer Cell Lines

Figure 1: The structure of IBL-302 is a first-class oral kinase inhibitor rationally designed to uniquely target PI3K, AKT and mTOR in a single agent. IBL-302 has been tested in over 700 cell lines with activity shown across a broad range of tissue types. Initial analysis of this cell line panel identified PHOSA mutation, high PIK kinase expression and elevated MYC expression as factors indicating sensitivity to IBL-302, markers which may be supportive in selecting patient subgroups in clinical trials.

METHODS

- Figure 2: Sanger Institute GDS screening panel of more than 700 different cancer cell lines in a CellTiter Glo anti-proliferation assay (72hr incubation).
- Figure 3: (A) T-test comparing HER 2 AMP (Green), ECR (Orange) and TNBC (Blue). Each cell line’s corresponding PIM expression, MYC expression, MYC amplification, PTEN loss, PIK3CA mutation, EFR and PI-II status is displayed in the table.
- Figure 4: Treatment with IBL-302 (50ng/ml) for 21-days BT474 (C) and HCC1954 (D) in xenograft model versus vehicle controls in BALB/c nude mice.
- Figure 5: Proliferation assays were performed with IBL-302 at increasing concentrations with a stable Trastuzumab concentration (10µg/ml) across 7 different cells lines (A – G). Following 5-day incubation, during which control cells attained 80%-95% confluence, all media was replaced from the plates, and washed once with PBS. Proliferation was measured using the acid phosphatase assay.

EFICACY OF IBL-302 IN BT474/HCC1954 IN VIVO XENOGRFT MODELS

Figure 2: IBL-302 was tested in the Sanger Institute GDS screening panel of more than 700 different cancer cell lines in a CellTiter Glo anti-proliferation assay (72hr incubation). We subdivided a panel of 40 BC cell lines into their clinical subtypes; HER 2 AMP (Green), ECR (Orange) and TNBC (Blue). Each cell line’s corresponding PIM expression, MYC expression, MYC amplification, PTEN loss, PIK3CA mutation, EFR and PI-II status is displayed in the table.

STRATIFYING GROUPS BASED ON IBL-302 IC50

CONCLUSION

In conclusion, we have evaluated the preclinical activity of IBL-302 in a range of breast cancer models.

- IBL-302 has shown significant efficacy in a number of breast cancer cell lines in vitro and in vivo.
- We have stratified and identified a number of factors associated with increased IBL-302 sensitivity through statistical analysis (TNBC, MYC amplification & increased PIMI expression).
- Initial statistical analysis suggests IBL-302 could be effective in TNBC groups.
- In combination with Trastuzumab, IBL-302 demonstrated the best anti-proliferative effects in parental lines and in SKBR3 trastuzumab resistant cell lines with acquired resistance to Trastuzumab.
- Our results demonstrate the preclinical efficacy of IBL-302 as a single agent and in combination with trastuzumab in models of HER2-positive breast cancer. We believe that further studies assessing the impact of IBL-302 with novel HER2-targeted agents are warranted.

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